the vitamin D_2 compound paricalcitol, the PTH value is considered to be stabile when the patient's PTH value shows a thirty percent reduction, which reduction is stabile for at least 28 days. Thus, the **final dose** would be that dose of paricalcitol that was administered prior to the first stabile reduction in PTH values.

Finally, regression analysis is used to determine initial dose. One such method utilizes zero intercept linear regression. The zero intercept model is preferred for its ease of use by the medical professional as only one task must be completed which minimizes the risk of a mistake being made in the calculation. In this model, final dose is the response variable and baseline PTH is the predictor variable. It will be apparent to those skilled in the art that alternate regression models, e.g., multiple regression analysis, could also be employed to determine the initial dose.

Examples

Example 1 – Determination of Initial Dose (Model)

An exploratory analysis of a long-term open label study of paricalcitol injection (ZEMPLAR®, Abbott Laboratories) was performed in an attempt to discover a relatively safe and effective method of determining the starting dose of ZEMPLAR based on a patient's baseline PTH. Those patients who achieved a thirty percent decrease from baseline PTH for at least 28 days (4 weeks) were used in the analysis. The dose associated with the first thirty percent decrease (the final dose) of this PTH reduction period was determined. Using final dose as the response variable and a patient's baseline PTH as the predictor variable, a regression analysis was performed. A zero intercept model was employed so as to allow the physician a relatively easy method for determining the starting dose of the drug. The regression analysis

produced the following model for initial dose: initial dose (micrograms) equal to baseline PTH / 80.

The results are shown in Figures 1 and 2. Plot 1 provided in Figure 1 shows the observed dose vs. baseline PTH (dashed line) and the predicted dose vs. baseline PTH (solid line). Plot 2 provided in Figure 2 shows the difference in the observed dose and the predicted dose vs. baseline PTH.

The results show that the model will slightly underpredict the starting dose for lower values of baseline PTH. This may be desirable since patients with less significant hyperparathyroidism may benefit from less aggressive therapy.

Example 2 - Safety and Efficacy of Initial Dose

A double-blind, randomized, 12-week trial was conducted in 125 adult ESRD patients to determine if a starting dose of paricalcitol injection using baseline PTH/80 was equivalent in the rate of hypercalcemia (single episode, Ca >11.5 miligram/deciliter) compared to the approved initial dose (0.04 mcg/kg, dry weight). Patients were randomized (1:1) to doses by either PTH/80 or 0.04 mcg/kg. Baseline demographics and laboratory values were similar between groups. Dosing occurred 3× weekly per patient hemodialysis schedule. Dose increases of 2 mcg could occur once per 2 weeks; decreases of 2 mcg could occur once per week. Patients completed the study by reducing PTH ≥30% from baseline for 4 consecutive weekly measurements, or by having a single incidence of hypercalcemia, or by completing 12 weeks of treatment. The primary analysis was a comparison of the incidence of hypercalcemia between groups. Secondary analyses included the time in days to the first of 4 consecutive ≥30% decreases from baseline PTH levels, the difference in the number of dose adjustments to achieve the first of 4 consecutive ≥30% decreases

from baseline PTH levels, and the difference in the incidence rates of 2 consecutive occurrences of CaxP>75. Results are presented in Table 1.

Table 1

Parameter	**PTH/80**	**0.04 mcg/kg**
Incidence(s) of Hypercalcemia	0	0
Median Days to First of 4≥30% PTH Decreases*	31	45
Median Number of Dose Adjustments	2	3
Incidences of Ca x P >75	5	2
Mean PTH (pg/mL) Decrease (SE)	-259 (24.01)	-193 (24.59)

*Statistically significant (P=0.0306)

The safety profile (adverse events, laboratory results, vital signs) was similar between treatment groups. In conclusion, dosing based on the severity of hyperparathyroidism incurred no additional risk of hypercalcemia and proved a safe, effective, and simple alternative to dosing based on dry weight.